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Is It Necessary to Test Patients With Immune Thrombocytopenic Purpura (ITP) for Seropositivity to HTLV-1?

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HTLV-111 (HIV-1) has been shown to be associated with thrombocytopenia of a type resembling immune thrombocytopenic purpura (ITP). HTLV-1 is a retrovirus similar to HIV-l (HTLV-III) in a number of features, such as CD4 tropism. It is responsible for several clinical entities, including adult T-cell leukemia/lymphoma. The relationship, if any, of HTLV-1 and thrombocytopenia has not been systematically studied. To determine how frequently ITP patients are commonly infected with HTLV-1, the following study was performed. Frozen serum samples from 123 randomly selected patients with ITP were thawed and tested for antibodies to HTLV-1 by enzyme-linked immunoabsorbent assay. Positives were confirmed by Western blot. Three patients were initially found to be positive for HTLV-1. One was a female of Caribbean ancestry, one was a male HIV-1+ patient, and one was an adolescent female with no known risk factors for HIV-1. The two females later tested negative for HTLV-1. As a screening program for HTLV-1 antibodies was not introduced into blood banks until November 1988, there may have been passive transfer of the virus from intravenous immunoglobulin that these patients had received. This study of a large number of ITP patients shows that it is extremely unlikely that they are infected with HTLV-1, and, therefore, it is unnecessary to screen ITP patients for seropositivity to HTLV-1. Am. J. Hematol. 61:94–97, 1999. © 1999 Wiley-Liss, Inc.

Key words: HTLV-1; immune thrombocytopenia

INTRODUCTION

Human T-cell lymphotropic virus type I (HTLV-1) was the first recognized human retrovirus. It was identified in 1980 in T cells from patients with adult T-cell leukemia/lymphoma (ATLL) [1] and found to be endemic in southwest Japan, the Caribbean, Africa, the southeastern United States, and New Guinea [1,2]. The virus is transmitted sexually and by breast milk, intravenous drug use, and transfusions [1,2]. The seroprevalence of HTLV-I/II in blood donors in the United States was 0.017 to 0.058% in a study conducted from December 1988 to May 1989 [3]. In addition to ATLL, HTLV-1 is also thought to cause spastic paraparesis, polymyositis, and a rare severe infant dermatologic disorder [1,2,4,5].

HIV-1 was initially identified as HTLV-III. It was soon recognized to cause acquired immunodeficiency syndrome (AIDS), and also to be associated with both Hodgkin's and non-Hodgkin's lymphoma [6]. Of specific note for this report, HIV-1 is well known to be commonly associated with thrombocytopenia [7].

HIV-1 and HTLV-1 have important common features—CD4 cell tropism, extraregulatory genes, similar modes of transmission, and association with lymphoid malignancies [4,8]. Thrombotic thrombocytopenic purpura has been found in an HTLV-1 infected male of Japanese ancestry [9], and antibody to HTLV-1 has been demonstrated in a female with systemic lupus erythematosis (SLE) and thrombocytopenia [10], but no other coincidence of HTLV-1 and thrombocytopenia has been reported. The purpose of this report was to determine

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TABLE I. Characteristics of Thrombocytopenic Patients in the Study Population; *n* = 123

	Number	Percentage
Age		
<18 yr	43	35.0
≥18 yr	80	65.0
Sex		
Male	45	36.6
Female	78	63.4
Type of ITP		
Acute	40	32.5
Chronic	83	67.5
HIV-1 Status		
Positive	20	16.3
Splenectomized		
Yes	27	22.0
No	96	78.0

whether there is any association of HTLV-1 infection and immune thrombocytopenia.

METHODS

Patients

One hundred twenty three patients with "immune thrombocytopenic purpura" (ITP) seen at New York Hospital between 1981 and 1991, from whom sera had been obtained after written informed consent, were randomly chosen by a data coordinator uninvolved in the study, according to the following criteria: (1) there needed to be ample sera in the freezer so that additional testing would be possible if required; (2) there needed to be at least 20 patients in each of the following categories: HIV-1+ and HIV-l−, splenectomized and nonsplenectomized, children and adults, acute and chronic disease. The exact numbers in each group are indicated in Table I. ITP was defined by the American Society of Hematology guidelines [11] except in the case of the 23 HIV-1 infected thrombocytopenic patients. Patients were tested for HIV-1 if known to have one or more risk factors for HIV infection. Repeat specimens were assayed in patients who were positive.

HTLV-1 antibodies were assayed in duplicate by enzyme-linked immunoabsorbent assay (ELISA) (Abbott Labs, Chicago, Ill.). Positive samples were confirmed by Western blot (Cambridge, Worcester, Mass.). The two patients who seroreverted had their follow-up specimens tested by polymerase chain reaction (PCR), using primer pairs for *pol* sequence (SK110/SK111) and for *tax* sequence (SK43/SK44). PCR reagents were purchased from Promega (Madison, Wis.). PCR-amplified products were analyzed by liquid hybridization with specific internal probes labeled with ^{32}P ATP [12]. Caution for preventing PCR contamination was scrupulously observed.

RESULTS

Three of the 123 patients were found to be positive for HTLV-1 by ELISA and Western blot. One was an 8-year-old female of Caribbean ancestry, one was a male patient apparently infected with HIV-1 and HTLV-1 as a result of intravenous drug use, and one was an adolescent female with no known risk factors for HTLV-1.

Several serum samples taken six and nine years after the date of the initially tested specimens from the two females were consistently negative for antibody to HTLV-1. Both patients were also negative for HTLV-1 by PCR screening. These two patients had received intravenous immune globulin (IVIG) prior to the initial test specimen.

As shown in the table, at least 20 patients were tested in each of the following categories: HIV-l+, <18 yr, ≥18 yr, acute thrombocytopenia, chronic thrombocytopenia, and before and after splenectomy status. None of the 103 non-HIV infected patients with ITP tested positive for HTLV-1. The one positive result out of 123 gives a 95% confidence interval of 0 to 0.024.

DISCUSSION

The results of this study show that there is no reason to routinely test ITP patients who do not have specific risk factors for infection by HTLV-1. Only one of 123 ITP patients was HTLV-1 infected, and this HTLV-1 positive patient had one of the risk factors for this virus—intravenous drug use. This patient was also HIV-l+ and not taking antiretroviral medication, which probably explains his thrombocytopenia, further suggesting that there is no association of HTLV-1 and ITP.

Calculation of 95% confidence intervals implies that, at the most, 2.4% of thrombocytopenic patients comparable with those analyzed here would be HTLV-1 infected, based on one infected patient among 123. If this patient was excluded as discussed above, the chance of HTLV-1 infection in ITP patients would be even less. Since all categories of ITP were represented by at least 20 patients each, this lack of association cannot be explained by omission of a subset of thrombocytopenic patients.

Infection with HTLV-1 is believed to result in lifelong seropositivity [2]. Therefore, the two females who seroreverted must have been transiently antibody positive from IVIG. This was confirmed by the PCR testing. As a screening program for HTLV-1 antibodies was not in-

troduced into blood banks until November 1988 [13,14], there may have been passive transfer of the anti-HTLV-1 antibody from the intravenous immune globulin that the two females received in 1986 as therapy for their ITP. Transfusion of cellular blood products, but not plasma products, has been associated with the transmission of HTLV-1 [2]. Passive transfer of HIV-1 antibodies without true infection, as confirmed by subsequent seroreversion, has been reported with IVIG prior to HIV-1 screening [15].

HIV-1 is believed to cause thrombocytopenia by two mechanisms: (1) direct effects of HIV in the bone marrow, including infection of the megakaryocyte [16,17] and (2) immunodysregulation allowing production of auto-antiplatelet antibodies [7,18]. The latter may be similar pathophysiologically to classical ITP. Recently, Karpatkin has suggested that the antiplatelet antibodies, including immune complexes, are derived at least in part from anti-HIV antibodies binding to platelets in association with anti-idiotypic antibodies [18,19]. HIV infection of marrow megakaryocytes may impair the compensatory increase in platelet production as a result of thrombocytopenia [20,21].

HIV-1 belongs to a class of lentiviruses, which do not directly cause tumors, but commonly induce persistent, latent infections [4]. Unlike HIV-1, HTLV-1 does not induce loss of CD4+ cells, nor does it establish a latent phase; rather it causes unregulatable cell proliferation [8]. Even though HTLV-1 and HIV-1 both target CD4 cells, most people infected with HTLV-1 have an active and efficient immune response [22]. ITP has been linked with immunodeficiency states, such as common variable immunodeficiency [23], in addition to that associated with HIV-1. This failure of HTLV-1 to result in immunodeficiency could be one reason for the lack of ITP in individuals infected with this virus. Since HTLV-1 is not known to infect the megakaryocyte, it is possible that this is another explanation as to why HTLV-1 does not cause thrombocytopenia.

CONCLUSIONS

Because HTLV-1 infection and ITP are relatively rare conditions, our sample size is large enough to conclude that patients with ITP without risk factors for HTLV-1 do not need to be tested for HTLV-1. Despite their obvious similarities, structural and pathological differences between HTLV-1 and HIV-1 have been reported [8]. The lack of association between thrombocytopenia and HTLV-1 documented in this study demonstrates another way in which HTLV-1 and HIV-1 differ in their in vivo effects.

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